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10/643,141	08/18/2003	Stephen L. Hutcherson	C01037.70049.US	3287

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
02/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/643,141	HUTCHERSON ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 26-48 are under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on November 5, 2007 was filed after the mailing date of the first action on the merits after an RCE on May 16, 2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Objections Maintained

3. The objection to the specification as failing to provide antecedent basis for the phrase "wherein the phosphorothioate oligonucleotide is non antisense" is maintained.

The response filed November 19, 2007 has been carefully considered but is deemed not to be persuasive. The response states that paragraph 0016 of the specification teaches "It has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. This immunostimulation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess." The term cannot lack antecedent basis in the specification, when it is an important part of the discovery of the invention (see response page 9).

In response to this argument, the statement that the immunostimulation does not appear to be related to any antisense affect does not provide support for the term "not antisense". As cited in the office action dated February 27, 2006, the specification states the present invention employs phosphorothioate antisense oligonucleotide analogs which elicit a local inflammatory response (see page 3 of action and page 10 lines 16-18 of the as-filed specification). The specification does not use either the terms "sense" or "not antisense" in describing the analogs of the invention.

Therefore, after a fresh consideration of the claims and the evidence provided, the objection is maintained.

Rejections Maintained

4. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking written description is maintained.

The response filed November 19, 2007 has been carefully considered but is deemed not to be persuasive. The response states that Applicant has previously respectfully disagreed with this broad interpretation of McIntyre (see Applicant's remarks in the amendment dated July 25, 2006, page 6, paragraph 2). McIntyre teaches only one nucleotide, for which the data were interpreted as indicating a sequence-specific immune effect. However McIntyre later proposes other possible explanations for the data (McIntyre, p318). Therefore, McIntyre does not broadly teach that phosphorothioate oligonucleotides do not elicit non-specific effects or immune responses. In addition, the claimed invention is limited to a cell-mediated immune response. As the teachings of McIntyre are directed to a humoral immune response

these teachings are therefore not directly applicable to claims directed to a cell-mediated immune response (see response page 5).

In response to this argument, McIntyre was cited to illustrate that applicant was not in possession of a representative number of species of the broad genus of phosphorothioate analogs at the time the invention was made. McIntyre teach sequence specific effects of phosphorothioate analogs and Wu et al. (also cited in the initial rejection dated February 27, 2006) teach phosphorothioate analogs interact non-specifically with cellular targets, thus the interaction is not sequence specific (see office action page 4). Therefore, the antisense analogs described in the specification are not representative of the entire genus of phosphorothioate analogs wherein the phosphorothioate analog is not antisense.

Thus, after a fresh consideration of the claims and the evidence provided, the rejection is maintained.

5. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

The response filed November 19, 2007 has been carefully considered, but is deemed not to be persuasive. The response states that the Examiner cites Crooke (Bio/technology 1992 Vol. 10 No. 8 pages 882-886) as teaching that the "activity of ISIS 1082 [is] equivalent to trifluorothymidine in cornea of mice, but less active in other animal models" to support her argument that Applicant has not enabled the claimed genus. However, Crooke et al. does not make clear whether ISIS 1082 is being compared to trifluorothymidine in other mouse models or used alone, what the other

mouse models are (such as whether they are models of a condition for which immunostimulatory phosphorothioate oligonucleotide analogs would be useful for treatment), or whether the method of administration was topical application to the cornea as in Crooke or some other method of administration. The claimed phosphorothioate oligonucleotide analogs are described as immunopotentiators. Page 10 line 36 - page 11 line 7 of the specification states that "[i]n the context of this invention, the term "immunopotentiator" refers to a material which produces non-specific immune stimulation. Immune stimulation can be assayed by measuring various immune parameters, for example antibody-forming capacity, number of lymphocyte subpopulations, mixed leukocyte response assay or lymphocyte proliferation assay. Immune stimulation may result in increased resistance to infection or resistance to tumor growth upon administration." Therefore, administration of the phosphorothioate oligonucleotide analogs results in a general immune stimulus that is useful for treating conditions that respond to an elevated immune response such as cancer or infectious disease. Furthermore, the specification provides guidance for the administration of the phosphorothioate oligonucleotide analogs (see pages 13-14 of the specification). The Examiner has stated that the "specification discloses the phosphorothioate molecules to be antisense or complementary to viral RNAs; thus the oligos used in the examples cannot be not-antisense as claimed". The Examiner cites Branda (Biochemical Pharmacology (1993) Vol. 45 No. 10, pages 2037-2043), which teaches antisense molecules, as being the closest prior art. While the instant specification discloses phosphorothioate oligonucleotide analogs that are antisense molecules, it also teaches that these molecules have a second property, sequence non-specific immune

stimulatory capacity. Page 8, lines 23-28 of the instant specification teach that it has "been found that oligonucleotide analogs having at least one phosphorothioate bond can be used to induce stimulation of a systemic or humoral immune response. Thus, these oligonucleotides are also useful as immunopotentiators of an antibody response, either alone or in combination with other therapeutic modalities." (see response pages 5-8)

In response to this argument, Crooke, et al. was cited in addition to the arguments and references cited in previous office action (see office action dated May 16, 2007 page 4). There were seven additional references cited in prior office actions to support the state of the art regarding phosphorothioate analogs and that not all phosphorothioate analogs are immunostimulatory. Crooke, et al. merely adds to the argument that in addition to not all phosphorothioate analogs being immunostimulatory, the same phosphorothioate analog reacts differently in different model systems. Regarding the working examples provided in the specification, the examples demonstrate that the antisense phosphorothioate analog of ISIS 2105 induced an antibody response. The examples do not provide evidence to support the mechanism that this response is not related to antisense effects of the analog. Thus, undue experimentation would be required to perform the claimed methods with a reasonable expectation of success through a non-antisense mechanism.

Therefore, after a fresh consideration of the claims and the evidence provided, the rejection is maintained.

6. The rejection of claims 26, 28, 29, and 30 as being unpatentable over claims 1-8 of US Patent 6,727,230 (Hutcherson, et al.) in view of US Patent 5,356,882 (Walker, et al.) is maintained.

The response filed November 19, 2007 has been carefully considered but is deemed not to be persuasive. The response states that applicants may consider filing a Terminal Disclaimer if some claims are found to be allowable (see response page 9).

In response to this argument, since the claims have not been found to be allowable and a Terminal Disclaimer has not been filed, the rejection is maintained.

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

February 11, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643